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AWARD NUMBER DAMD17-97-1-7072

TITLE: DNA Repair and Breast Cancer Risk

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CONTRACTING ORGANIZATION: Johns Hopkins University
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REPORT DATE: October 1998

TYPE OF REPORT: Annual

PREPARED FOR: Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 1998	Annual (1 Oct 97 - 30 Sep 98)

4. TITLE AND SUBTITLE

DNA Repair and Breast Cancer Risk

5. FUNDING NUMBERS

DAMD17-97-1-7072

6. AUTHOR(S)

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Johns Hopkins University
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research And Materiel Command
ATTN: MCMR-RMI-S
504 Scott Street
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

Investigations of potential gene-environment interactions may improve our understanding of the etiology of breast cancer, a disease where less than 40% of cases can be attributed to known risk factors. The objectives of this study are to examine the association between DNA repair proficiency and breast cancer risk, and the contribution of this factor to the familial clustering of breast cancer. We hypothesize that mechanisms leading to suboptimal repair of DNA damage are susceptibility factors predisposing women to breast cancer through increased sensitivity to carcinogenic damage from environmental exposures such as ionizing radiation.

To evaluate this hypothesis a case-control study and a family study are being conducted. Women with a personal history of breast cancer (N=100) and women at increased breast cancer risk (N=100) will be compared to control women (N=100) with respect to their ability to repair ionizing radiation-induced DNA damage in lymphocytes. We will also evaluate the possible interaction between DNA repair proficiency and ionizing radiation exposure by stratifying the case-control data on exposure status and then assessing the relationship between breast cancer risk and DNA repair proficiency. Thirty to forty families (150 family members) will be recruited to participate in the family study. The family study is designed to assess the segregation of DNA repair proficiency in families of women with suboptimal DNA repair proficiency, and, in a preliminary way, the co-segregation of breast cancer and suboptimal DNA repair proficiency in these families.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Breast Cancer , DNA Repair	51
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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Kathy J Hilgemann 10/26/98

PI - Signature Date

TABLE of CONTENTS

1. INTRODUCTION

1.1 Objective

The purpose of the study is to assess whether suboptimal repair of DNA damage is associated with increased breast cancer risk, to assess the possible interaction between DNA repair proficiency and ionizing radiation exposure, and to evaluate the inheritance pattern of suboptimal DNA repair proficiency.

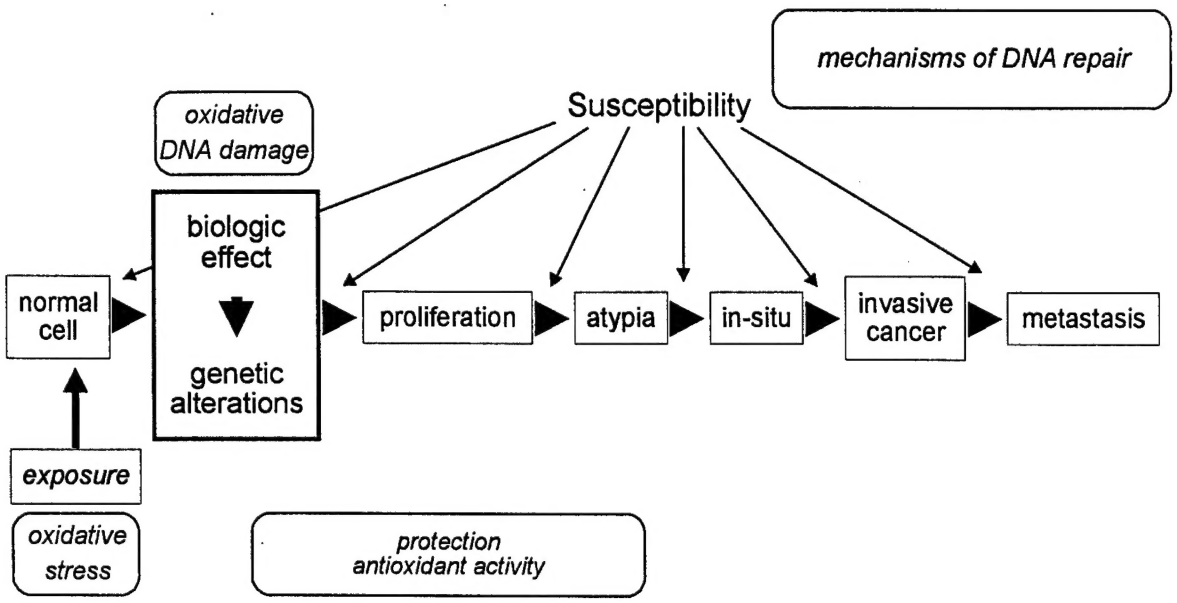
1.2 Background

New clues are desperately needed to improve our understanding of the etiology and possible methods of preventing breast cancer. Breast cancer is the leading type of cancer and the second leading cause of death from cancer among women in the United States. Fewer than 40% of all breast cancer cases can be explained by known risk factors (1), and the incidence of breast cancer continues to rise. From 1973 to 1991 incidence rates have risen approximately 24% (2). That most of this increase is due to an increase in screening and lead time effects is suggested by the increased incidence of early stage disease as well as increased mammography utilization (3-5). However, an increase in the incidence of breast cancer of approximately 1% per year has been noted in Connecticut since 1940 (6)—years before screening or exogenous hormones were in use—suggesting that these two factors alone do not account for the increase in incidence.

Breast cancer can cluster in families, the etiology of which may be related to both genetic and environmental factors. An autosomal dominantly inherited predisposition to breast cancer appears to be segregating in some high-risk families (7); several cancer susceptibility loci (BRCA1, BRCA2, and possibly BRCA3) have been identified that can confer greatly increased breast cancer risk (8,9). However, this mode of transmission of breast cancer susceptibility accounts for only 5-10% of breast cancer cases, and is not sufficient to explain all of the observed familial clustering of breast cancer (7,10). Other factors that have been linked to increased breast cancer risk include older age, younger age at menarche, older age at first birth, older age at menopause, fibrocystic disease, radiation exposure, exogenous hormone use, alcohol use, and high fat intake (11,12). But again, this long list of risk factors explains less than 40% of breast cancer cases (1). Studies investigating the potential interactions between genetic and other susceptibility factors and environmental exposures are necessary to increase our understanding of breast cancer etiology and to develop new intervention models to decrease breast cancer risk and/or mortality.

The study will evaluate possible gene-environment interaction in breast cancer development. A hypothetical schema for the multi-stage process of breast carcinogenesis leading to breast cancer is shown in Figure 1 (13-15). Factors involved in this complex process can be broadly classified into exposures (endogenous and exogenous), susceptibility factors (inherited or acquired), and modifying and/or protective factors. This project will examine the association between DNA repair mechanisms, a proposed susceptibility factor, and breast cancer risk. Once this association is established, the long-range goal is to conduct an expanded study to examine the association of DNA repair mechanisms, level of oxidative stress (exposures), and antioxidant activity (protective factor).

Figure 1. Relationship among susceptibility factors (e.g., DNA repair mechanisms), exposures (e.g., oxidative stress), and protective factors (e.g., antioxidant activity) in the development of breast cancer



DNA repair systems were voted the "molecule of the year" by *Science* (16). DNA is continually damaged by endogenous mechanisms such as products of oxidations, as well as exogenous exposures to carcinogens such as ionizing radiation. Repair of the damage is critical in preventing the genetic alterations of the carcinogenic process. The proposed study examines the ability to repair ionizing radiation-induced damage of lymphocytes as a susceptibility factor for breast cancer.

Ionizing radiation is well established as an etiologic agent for breast cancer among persons with relatively high-level exposures (17-22). In addition, some persons may be at increased breast cancer risk after low-level exposures to irradiation. A higher breast cancer rate has been observed among female biologic relatives of persons with ataxia telangiectasia (AT) compared with married-in female relatives (23). AT is an autosomal recessively inherited syndrome associated with cellular hypersensitivity to ionizing radiation. Increased levels of chromosomal breaks and gaps in lymphocytes following ionizing radiation exposure have been demonstrated in individuals presumably heterozygous for an AT gene (24). Therefore, the observed increased breast cancer risk among AT heterozygotes may be a result of increased sensitivity to lower-level irradiation exposure as a result of poor DNA repair. The frequency of heterozygotes for an AT gene in the general population is estimated to be 1-2%.

Quantitation of DNA damage after exposure to mutagenic agents could effectively detect individuals with defective repair mechanisms. Hsu et al. showed that by exposing cultured human lymphocytes from normal individuals and patients with cancer to bleomycin, different frequencies of chromatid lesions are observed (25). This was interpreted as secondary to differences in DNA repair capability. Sanford et al. have shown higher occurrence of chromatid gaps and breaks after

ionizing radiation-induced damage in cultured skin fibroblasts or peripheral blood lymphocytes in many individuals with chromosome breakage syndromes (26), as well as with hereditary tumors (27). They have also detected a two-to-three fold higher frequency of chromosome aberrations in presumed AT heterozygotes than in normal controls (24). Many individuals in the population may have subtle defects in one of many responses to DNA damage, such as mild defects in DNA repair or cell cycle arrest after DNA damage, that place them at risk of developing cancer. Functional assays to evaluate the status of repair systems have the potential to be used as screening tools to detect individuals who may have an increased susceptibility to carcinogenic exposures and thus be at increased cancer risk.

1.3 Hypothesis/Purpose

We hypothesize that mechanisms leading to suboptimal DNA repair proficiency are susceptibility factors predisposing women to breast cancer through increased sensitivity to carcinogenic damage from environmental exposures such as ionizing radiation. We are measuring DNA repair proficiency in lmphocytes following irradiation using the method developed by Sanford and Parshad (24). We are using this method because previous studies link this measure to a variety of cancers; it can distinguish AT heterozygote cell lines from normal cell lines; and it uses ionizing radiation as the method of DNA damage (24,26,27,28). In addition, the results of the assay have a bimodal distribution (24,28). This presents a distinct advantage in classifying suboptimal versus optimal repair and avoids the need to establish an arbitrary cut-off point.

1.4 Technical Objectives

Conduct a case-control study and a family study to address the following research questions:

1. Do women with breast cancer and women with a family history of breast cancer more often have suboptimal repair of DNA damage compared to control women?

2. Does suboptimal repair of DNA damage cluster in families?

1.5 Study Design

1.5.1 Case-control study

The case-control study design is clinic-based. We have two case groups: 1) women with newly diagnosed breast cancer and 2) women with a family history of breast cancer in at least one first-degree relative or two-second degree relatives on either the maternal or paternal side of the family. Cases are recruited from the Breast Center of the Johns Hopkins Cancer Center, and the Breast and Ovarian Surveillance Service (BOSS), which is part of the Breast Center. The primary reason that women attend BOSS is to obtain risk assessment and counseling because of a family history of breast cancer. The Breast Center shares an office suite with the physician practices of the outpatient gynecologic services of the Johns Hopkins Hospital, and we recruit controls from women attending these gynecologic services. The Breast Center, BOSS, and the outpatient gynecologic services serve a similar catchment area which includes the Baltimore Metropolitan Region. The study base principle for case-control studies, that cases and controls be "representative of the same base experience" (29), should, therefore, be satisfied. To satisfy this

requirement, two assumptions should be met: cases and controls should be selected from identical catchment populations, and exposure should be independent of admission or clinic attendance. The catchment population is similar for the clinics. In this study we are studying DNA repair proficiency as the exposure of interest. DNA repair proficiency is not known for any disease, thus it cannot influence attendance at the clinics.

1.5.2 Family study

The family study of DNA repair proficiency and breast cancer occurrence is designed to assess the segregation of DNA repair proficiency in families of women with suboptimal proficiency, and, in a preliminary way, the co-segregation of breast cancer and suboptimal DNA repair proficiency in these families. The family study is an important follow-up to the case-control study. Once we confirm the association between DNA repair proficiency and breast cancer risk that our preliminary data suggest, it will be important to understand the inheritance of variation in DNA repair proficiency and the degree to which it can explain the clustering of breast cancer among family members. We anticipate that, if inherited, such cancer susceptibility will be transmitted as an autosomal dominant trait. Individuals who are homozygous for cancer susceptibility genes (e.g., ataxia telangiectasia) are clinically recognizable, often die at a young age, and would not be included as study participants. However, individuals who are carriers of such genes may be at increased cancer risk and may pass this gene on to their children. In such instances, cancer susceptibility is transmitted as an autosomal dominant trait.

1.6 Methods

1.6.1 DNA repair assay

We are measuring DNA repair proficiency according to the method developed by Sanford and Parshad (24). For each sample assayed, fifty metaphase cells are examined for chromatid damage (breaks and gaps).

1.6.2 Participant selection for the case-control study

DNA repair proficiency will be compared among three groups of women: 1) with newly diagnosed breast cancer; 2) with a family history of breast cancer, and thus at increased breast cancer risk; and 3) without cancer and without a significant family history of cancer. One hundred women will be recruited to each group.

Incident breast cancer cases are recruited from women attending the Breast Center at the Johns Hopkins Oncology Center. Over 500 women with newly diagnosed breast cancer are seen each year at the Breast Center. Eligible women are newly diagnosed, over the age of 20, without a previously diagnosed cancer other than nonmelanoma skin cancer, and not currently under adjuvant therapy. Women with metastatic breast cancer will be excluded. The diagnosis of all women seen at the Breast Center is confirmed by review of pathologic specimens. Women with pre-menopausal and with post-menopausal onset of breast cancer are included.

Women at increased breast cancer risk are recruited from the Breast and Ovarian Surveillance Service (BOSS). The Breast and Ovarian Surveillance Service offers clinical risk assessment, screening and prevention counseling to women at increased breast cancer risk due to a family history of breast cancer and/or the presence of proliferative benign breast disease. The service follows over 400 women at increased breast cancer risk and sees approximately 2 to 3 new

women per week. Women range in age from 16 to 70 with a mean age of 37. The average 10-year risk of breast cancer for women attending the clinic is 8%, based on the model developed by Gail et al. (30). This compares to a 10-year risk of 2.5% for the average 50 year old woman. The high-risk group will include women with: 1) at least one first-degree relative with breast cancer, or 2) at least two second-degree relatives with breast cancer on the same side of the family. Eligible women will be over the age of 20 and without a previous diagnosis of cancer, other than nonmelanoma skin cancer.

Each woman attending the Breast Center or the Breast and Ovarian Surveillance Service will be given a brochure describing the study. Ms. Perry, the study coordinator, will review the medical records of each woman attending the Breast and Ovarian Surveillance Service to assess eligibility; after this screening, each potentially eligible woman will be contacted to further assess eligibility and willingness to participate in the study. In our preliminary study, 99% of women approached participated in the study—completing a questionnaire and donating a blood sample.

Controls will be recruited from women attending the Faculty Practices of the Johns Hopkins Medical Institutions Gynecology Service for routine outpatient visits. The gynecology practice facility is immediately adjacent to the Breast and Ovarian Surveillance Service and serves a similar patient population. Eligible women will be those over the age of 20, without a prior diagnosis of cancer other than nonmelanoma skin cancer, no history of proliferative breast disease with atypia, an "insignificant" family history of breast cancer (i.e., breast cancer occurring in at most one second-degree relative on each side of the family), and no history of other cancers in first-degree relatives. Cases and controls will be frequency age-matched (<50 and ≥50 years) as a surrogate for menopausal status during recruitment, so that differences in the associations between pre- and post-menopausal women can be evaluated. Controls will be selected at random from patient lists of potentially eligible women attending the gynecology clinic on the same day as recruitment of high-risk women, stratified on age (<50 and ≥50 years).

Women who are scheduled to attend the gynecology practice for a routine visit and who are in the appropriate age group will be sent a brochure describing the study. Ms. Perry, the study coordinator, will contact potential participants to assess their willingness to participate and their eligibility.

1.6.3 Participant selection for the family study

About 150 family members from 30-40 families will be recruited to the family study. We will target families of high-risk case participants in the case-control study who have suboptimal repair proficiency for radiation-induced DNA damage (i.e., the probands for the family study). In this way, we know that the trait, if inherited, is segregating in the family. This definition of probands will also provide families in which to study the co-segregation of breast cancer and DNA repair proficiency, since, by definition, cases will have relatives with breast cancer. We will exclude families in which the proband is an only child and does not have any adult children (or will not permit us to contact her siblings and adult children); such families provide little information about the segregation of DNA repair proficiency. Although breast cancer is rare in men, men as well as women will be included in the family study since there is no evidence (or biologic reason) that expression of DNA repair proficiency is affected by gender. Inclusion of men along with women will facilitate assessment of segregation patterns by increasing sibship sizes and minimizing missing data on parents.

Families in which the cancer family history is so strong that they appear to represent "inherited" breast or breast/ovarian cancer families (at least three relatives with breast and/or

ovarian cancer, at least two of which are first degree relatives, in three generations), or have a rare cancer syndrome such as Li-Fraumeni syndrome, will be excluded. From published information about the frequency of major genes (such as mutations in BRCA1), we expect that these families will represent no more than 10% of eligible probands. BRCA1/BRCA2 mutation testing will not be part of this study's protocol. Probands from these very-high-risk families will referred to the Breast and Ovarian Surveillance Service to obtain more information about genetic testing for cancer susceptibility.

Probands from eligible families will be recontacted and asked to give us permission to contact all adult first-degree family members (parents, siblings, and children), and their children's biologic father(s), if their adult children are willing to participate. If permission is given, the proband will be asked to provide contact information for all first-degree relatives and, if appropriate, her partner(s). A letter will be sent to each family member to describe the study, with telephone follow-up to find out if the relative is willing and able to participate. Geographic location should not be a barrier since blood samples can be mailed, and questionnaires can be completed by mail or over the telephone. Family members currently under chemotherapy, radiotherapy, or hormonal treatment for cancer will be asked to provide a blood sample once the treatment has been completed, if feasible within the time frame of the project.

1.7 Background of previous work

We investigated a cluster of breast cancer cases among sisters as a preliminary method to evaluate our hypothesis that suboptimal repair of DNA damage may be a susceptibility factor predisposing women to breast cancer through increased sensitivity to carcinogenic damage from environmental exposures, such as ionizing radiation (31). This family differs from other reports of families with high cancer incidence in that breast cancer clustered in one generation among those with known exposure to ionizing radiation (repeated chest fluoroscopic examinations) during adolescence and early adulthood. Persistence of chromosomal damage (breaks + gaps >60) following irradiation to lymphocytes was measured in several family members, using the method developed by Sanford and Parshad (24), and correlated with the history of radiation exposure. The pattern of breast cancer occurrence and evidence of suboptimal repair of DNA damage was consistent with the hypothesized gene-environment interaction, but not conclusive. Two of the three surviving sisters with breast cancer had low-level exposure to fluoroscopies but had suboptimal repair of DNA damage. The other surviving sister with breast cancer did not have evidence of suboptimal DNA repair but had a very high radiation exposure that one could hypothesize would overwhelm even normal DNA repair processes.

Following this investigation, we conducted a pilot study to examine the frequency of suboptimal DNA repair among women with breast cancer, women at high-risk of breast cancer, and controls. We have studied 40 women: 4 with breast cancer, 17 with a family history of breast cancer, and 19 controls (32). All 4 women with breast cancer had suboptimal repair of radiation-induced DNA damage of lymphocytes compared to 72% of high-risk women and 32% of control women. Thus, women with a family history of breast cancer are much more likely than control women to have evidence of suboptimal repair of ionizing radiation-induced DNA damage (odds ratio=5.2, 95% confidence interval=1.04, 28.6). In a study by Knight et al., 22% of 60 individuals without cancer had evidence of suboptimal repair (28).

2. BODY: PROGRESS REPORT YEAR 1

2.1 Technical Objective 1: Case-control study

Task 1: Develop and produce study brochures. Finalize questionnaires.

We developed study brochures for recruitment to the case control study. (Appendix 1). We finalized the medical history questionnaire for women recruited to the case-control and family studies, and developed a similar questionnaire for male family members who participate in the family study. (Appendix 2). We finalized the family history questionnaire (Appendix 3). We developed a database in Paradox to assist in recruitment.

Task 2: Identify and recruit eligible participants (300 cases and controls).

Task 3: Collect questionnaire data and blood samples.

We developed a screening form to identify and recruit participants to the case-control study (Appendix 4), and physicians and nurses in the Breast and Ovarian Surveillance Service and the Breast Center agreed to help us recruit women to the study. We recruit controls from the physician practices of the outpatient gynecologic services. The gynecology facility is immediately adjacent to the Breast and Ovarian Surveillance Service and serves a similar patient population.

We are measuring DNA repair by the method developed by Sanford and Parshad (24). We used this method in our pilot study in 1993-5. It was necessary to verify replication of the assay in our laboratory before recruiting participants, since our pilot samples were assayed in a lab at NIH. We obtained samples from volunteer donors beginning December 1997, and recruited women to the case-control study starting in June, but stopped recruiting in July due to detection of problems related to repeatability of the assay. At present recruitment is on hold, pending resolution of problems with the assay (see Task 4).

In order to test our assay we are recruiting individuals who are ataxia telangiectasia heterozygotes, because these individuals are known to have poor repair in this assay, to give blood to be used as a laboratory control in the assay. We are recruiting these individuals, parents of children diagnosed as having ataxia telangiectasia, with the permission of Dr. Howard Lederman, of the Ataxia Clinical Center at Johns Hopkins.

We started collecting questionnaire data and blood samples in June, and will resume collecting questionnaire data and blood samples as soon as we resume recruitment.

Task 4: DNA repair assays

We are measuring DNA repair proficiency according to the method developed at NIH by Sanford and Parshad (24). We used this method in our pilot study in 1993-5, when we sent samples to be assayed in Dr. Sanford's lab at NIH. Lymhocytes were stimulated with PHA on day one, and incubated for 72 hours before irradiation with 58 cGy ionzing radiation on day four. Cells were allowed to repair at 37^0C for 0.5 hour without colcemid, then for 1 hour with colcemid,

to arrest cells in metaphase. On days 5-7, cells were lysed and fixed, and slides prepared, stained, and fixed. On day 8 or later, slides were examined to identify fifty metaphase (dividing) cells, and the metaphase cells were examined for chromatid damage (breaks and gaps). Chromatid breaks show a discontinuity with displacement of the broken segment. Chromatid gaps show a discontinuity with no displacement, and were scored only if the discontinuity was longer than the chromatid width.

Before we could begin to assay case-control samples, we had to transfer the DNA repair assay from the lab at NIH to our lab. Transferring the assay to our lab in 1997 required adapting the assay from an ionizing radiation source to a gamma (cesium chloride) radiation source, because an ionizing source was not available. To test gamma radiation doses in our lab, we irradiated PHA stimulated lymphocytes from donor 100, a donor with good repair eleven times at NIH in our 1993-5 pilot study. We irradiated cells with 25 and 50 cGy gamma radiation, and allowed irradiated cells to repair for the same time allowed at NIH, i.e., for 0.5 hour without colcemid, then for 1 hour with colcemid. In four assays in our lab between December 1997 and April 1998, cells irradiated with 50 cGy gamma radiation had half or fewer metaphase cells after repair time and colcemid treatment as cells irradiated with 25 cGy, indicating that the higher radiation dose resulted in fewer metaphase cells, which may be due to mitotic block or cell killing. Therefore we decided to use the lower dose, 25 cGy, in our assays. Breaks and gaps are in Table 1.

Table 1. Best gamma radiation dose: Chromatid breaks and gaps after 25 cGy gamma irradiation[1]

Date of assay	Assay ID numbers	Donor blood assayed	Breaks and gaps per 50 metaphase cells	Repair status in our pilot study at NIH lab
12/5/97	JHU 1	100	Contaminated	Good repair
12/12/97	JHU 2	100	26	Good repair
12/22/97	JHU 3	100	32	Good repair
4/13/98	JHU 8	100	37	Good repair
4/20/98	JHU 9	100	20	Good repair

[1] Cells were allowed to repair for 1.5 hours with colcemid added at 0.5 hour.

In January through March we tested five repair times between 0.5 hour and 2.5 hours, in donor 100 and two other donors, for best time for repair, and found that 1.5 hours of repair time, with colcemid added at 0.5 hour, was the best time for repair in our assay. This is the time for repair used at NIH.

In April we looked at the effect of gamma radiation on cells from a donor who had poor repair when assayed at NIH in our 1993-5 pilot study, to test the reproducibility of our assay. We included cells from donor 100, who had good repair at NIH, as a control in the assay, and irradiated with 25 cGy gamma radiation. Results were consistent with the assay performed ar NIH.

In May and June we irradiated and assayed donors' lymphocytes in triplicate, to test repeatability, and chilled one of three tubes after repair time, before returning to our lab to lyse and fix cells (Table 2). Repeatability was very good in these assays. Donor 100 had 18, 19, and 16 breaks and gaps per fifty metaphase cells when assayed in triplicate in May; and 14, 15,

and 16 breaks and gaps when assayed in June. These numbers indicate good repair in this donor who was assayed multiple times at NIH and always had good repair. Donor 101, never assayed at NIH, had 16, 18, and 18 breaks and gaps per fifty metaphase cells. Donor 104, who had poor repair at NIH, had 35, 30, and 34 breaks and gaps per fifty metaphase cells, about two times the breaks and gaps we found in cells from donors 100 and 101.

Table 2. Repeatability: Chromatid breaks and gaps, and repair status, in donors assayed in triplicate

Date of assay	Assay ID numbers	Donor blood assayed	Breaks and gaps per 50 metaphase cells	Repair Status	
				Pilot study at NIH lab	Our lab
5/11/98	JHU 10	100	18, 19, 16	Good	Good
		101	16, 18, 18	Not done	Good
6/1/98	JHU 11	100	14, 15 ,16	Good	Good
		104	35 ,30 ,34	Poor	Poor

Because of good results in our repeatability assays, we started recruiting patients to the case-control study in June and July (Table 3). We included donor 100 in two of these assays, as a standard for good repair, and found that she had good repair, 13 breaks and gaps, in our June assay, but poor repair, 37 breaks and gaps, in July. We stopped recruiting patients to figure out why this donor wiho had good repair at NIH and previously in our lab, had poor repair in our July assay. Also, donor 105, who had good repair at NIH, had poor repair, 49 breaks and gaps, in July. In August, donor 100 had good repair in two assays, but two donors with poor repair at NIH had good repair in our lab (Table 4).

Table 3. Patient recruitment started: Chromatid breaks and gaps, and repair status

Date of assay	Assay ID numbers	Donor blood assayed	Breaks and gaps per 50 metaphase cells	Repair status	
				Pilot study at NIH lab	Our lab
6/29/98	JHU 12	100	13	Good	Good
		Pt 1 with FHX of BRCA[1]	33	Not done	Poor
7/13/98	JHU 13	105	49	Good	Poor
		106	34	Poor	Poor
		Pt 2 with FHX of BRCA[1]	35	Not done	Poor
		Pt 3 with FHX of BRCA[1]	31	Not done	Poor
7/27/98	JHU 14-15	100	37	Good	Poor
		Pt 4 with FHX of BRCA[1]	38	Not done	Poor

[1] Patient with family history of breast cancer.

Table 4. Patient recruitment stopped: Re-test of repair status in donors assayed in our pilot study at NIH lab

Date of assay	Assay ID numbers	Donor blood assayed	Breaks and gaps per 50 metaphase cells	Repair status	
				Pilot study at NIH lab	Our lab
8/7/98	JHU 16-19	100	15	Good	Good
		103	13	Poor	Good
8/21/98	JHU 20-23	100	16	Good	Good
		102	13	Poor	Good

The inconsistent results in our assays made us review all aspects of the assay, and we are optimizing conditions for good repair in the assay. Possible conditions leading to inconsistent results include changes in temperature and pH of the media during repair time, and contamination (33).

To optimize conditions for good repair, we are:

1. Using a 37°C warm room, which became available to us in September, for all repair time.

2. Equilibrating media for the assay with 10% $C0_2$ in air, instead of 5% $C0_2$, to better maintain a pH near 7.

3. Optimizing conditions to minimize the risk of contamination.

4. Recruiting individuals who are ataxia telangiectasia heterozygotes, i.e., parents of children diagnosed as having ataxia telangiectasia, to give blood to be used as a laboratory control for poor repair, because these individuals are known to have poor repair in this assay.

We are hoping to establish reproducibility of the assay by December and restart recuitment. In the midst of our difficulties, Dr. Ram Parshad, who analyzes the metaphase cells, had emergency bypass surgery in September. This has prompted us to identify a backup cytogeneticist to be trained to examine slides. Dr. Parshad will resume reading of the assay by January 1, 1999.

Task 5: Enter data (questionnaires, DNA repair results).

We enter DNA repair results for each assay after metaphase cells are examined. We will enter questionnaire data when we resume recruiting women to the case-control study.

2.2 Technical Objective 2: Family study

The family study is dependent upon the case-control study and will begin once the assay is established and reruitment resumes for the case-control study. We developed a letter to recruit family members of probands from eligible families to the family study (Appendix 5).

3. CONCLUSIONS

Plans for the next year are as follows:

1. Resolve problems with DNA repair assay.
2. Resume recruiting case-control participants.
3. Start the family study.
4. Enter DNA repair results and questionnaire data.

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APPENDICES

Appendix 1: Study brochures

To recruit women newly diagnosed with breast cancer *(1 page)*

To recruit women with a family history of breast cancer *(1 page)*

To recruit women without cancer and without a significant family history of breast cancer *(1 page)*

Appendix 2: Medical history questionnaires

Questionnaire for *women* who participate in the Breast Cancer Risk Study *(10 pages)*

Questionnaire for *men* who participate in the Breast Cancer Risk Study *(10 pages)*

Appendix 3: Family History Form for Breast Cancer Risk Study *(7 pages)*

Appendix 4: Screening Form for Breast Cancer Risk Study *(1 page)*

Appendix 5: Letter to recruit family members to the family study *(1 page)*

BREAST CANCER STUDY

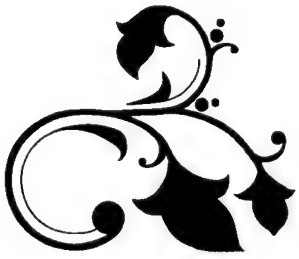
We are looking for women to help us with a study to learn more about the causes of breast cancer. The data from this study will be helpful to increase our understanding of who may be at increased risk for breast cancer. You may be eligible to help us with this study.

We need participants who

- Are newly diagnosed with breast cancer and have not yet started chemo, radiation, or hormonal therapy.
- Have not been previously diagnosed with any other cancer, other than basal or squamous cell skin cancer
- Are over the age of 20.

Participation involves donating a sample of blood and answering a questionnaire that you complete at home. Payment for participation is $15.00. For more information, or if you think you may like to participate, please call Helen Perry at 410-614-1112.

Department of Defense Grant BC962422
School of Hygiene and Public Health
Johns Hopkins University
Principal Investigator Kathy J. Helzlsouer, M.D., M.H.S.



BREAST CANCER STUDY

We are looking for women to help us with a study to learn more about the causes of breast cancer. The data from this study will be helpful to increase our understanding of who may be at increased risk for breast cancer. You may be eligible to help us with this study.

We need participants who:

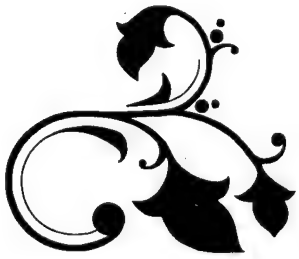
- Have not been diagnosed with breast cancer, or any other cancer other than than basal or squamous cell skin cancer
- Have at least one first-degree relative (parent, sister, brother, or child) diagnosed with breast cancer

  or

  At least two second-degree relatives (grandparents, aunts, uncles, nieces, or nephews) on the same side of the family, diagnosed with breast cancer
- Are over the age of 20.

Participation involves donating a sample of blood and answering a questionnaire that you complete at home. Payment for participation is $15.00. Some participants may be contacted later to participate in a family study. For more information, or if you think you may like to participate, please call Helen Perry at 410-614-1112.

Department of Defense Grant BC962422
School of Hygiene and Public Health
Johns Hopkins University
Principal Investigator Kathy J. Helzlsouer, M.D., M.H.S.



BREAST CANCER STUDY

We are looking for women to help us with a study to learn more about the causes of breast cancer. The data from this study will be helpful to increase our understanding of who may be at increased risk for breast cancer. You may be eligible to help us with this study.

We need participants who

- Have not been diagnosed with breast cancer, or any other cancer, other than than basal or squamous cell skin cancer
- Have no family history of breast cancer, or any other cancer, in parents, brothers, sisters, or children
- Have no family history of breast cancer in grandparents, aunts, uncles, nieces, or nephews, or breast cancer has occurred in at most one of these relatives on each side of the family
- Are over the age of 20.

Participation involves donating a sample of blood and answering a questionnaire that you complete at home. Payment for participation is $15.00. For more information, or if you think you may like to participate, please call Helen Perry at 410-614-1112.

Department of Defense Grant BC962422
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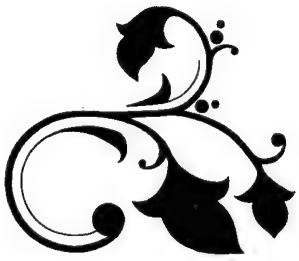

Questionnaire for *women* who participate in the Breast Cancer Risk Study, JH9243

Principal Investigator and Associates:
Kathy J. Helzlsouer, MD, MHS, Nancy Davidson, MD, Emily Harris, MPH, PhD

This questionnaire includes general medical and reproductive health questions, and questions concerning occupational exposures and tobacco and alcohol use. Answering each question is completely voluntary---you may skip questions that you do not want to answer. However, we hope that you will answer the questionnaire as completely as possible. If you need more space to answer a question, please use the back of the page.

Your questionnaire will be kept confidential and will not be given to anyone who is not helping with this study. Please call Helen Perry at 410-614-1112 if you have questions about the questionnaire or the study. Thank you for helping us learn more about the causes of breast cancer.

Your questionnaire is a very important part of the study. If you need a new envelope to return your questionnaire to us, please call Helen Perry at 410-614-1112. We will be glad to send you an envelope. If you wish to post your own envelope, please return the questionnaire to us at:

Johns Hopkins School of Public Health
615 North Wolfe Street
Baltimore, MD. 21205
Attn: Dr. Kathy Helzlsouer
Dept. of Epidemiology, Room 6132

Questionnaire for Breast Cancer Risk Study, JH9243

1. Today's date: ___ ___ /___ ___ /___ ___ ___ ___
   Month Day Year

2. Your name:

   _____
   First, Middle, Last *(Maiden Name)*

3. Address: _____
   Street

   _____
   City *State* *Zip Code*

4. Daytime phone: (___ ___ ___) ___ ___ ___ - ___ ___ ___ ___

5. Evening phone: (___ ___ ___) ___ ___ ___ - ___ ___ ___ ___

6. Date of birth: ___ ___ /___ ___ /___ ___ ___ ___
   Month Day Year

7. Marital Status *(Circle):* Single Married Widowed Divorced

8. Please circle the highest number of years of education you completed:

   1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 16+
   Highschool *College* *Post graduate*

9. What is your race/ethnic background?

   _____ White, non-Hispanic
   _____ Asian/Pacific Islander
   _____ African American
   _____ American Indian
   _____ Hispanic/Latino
   _____ Other, please specify: _____

10. Are you of Ashkenazi Jewish (Eastern European or Russian Jewish) descent?

    _____ Yes _____ No

11. What are the ethnic backgrounds of your parents?

    Mother: _____ Father: _____

12. Please complete the following table:

Have you ever had any problems with...	Yes	No	If yes, how old were you when you FIRST had this problem?	Are you CURRENTLY having problems with...	Yes	No
Breast lumps?	___	___	_____ Years old	Breast lumps?	___	___
Breast tenderness?	___	___	_____ Years old	Breast tenderness?	___	___
Drainage from nipple?	___	___	_____ Years old	Drainage from nipple?	___	___

13. Have you ever had a biopsy of the breast? _____ Yes _____ No --- **Go to Question 15.**

14. If yes, please complete the following table as completely as you can:

Year biopsy was done	**Type of biopsy done *(Check type.)***				**Result of biopsy**
	Removal of FLUID with a needle	Removal of TISSUE with a needle	Surgical biopsy	Not sure of type of biopsy	

15. Have you ever had any breast surgery, other than biopsies?

_____ Yes _____ No --- **Go to Question 17.**

16. If yes, what kind of breast surgery have you had?

_____

_____

_____

17. What is your height and weight?

Height: _____ Feet and _____ Inches Current weight: _____ Pounds

18. Have you ever been told by a doctor or other health professional that you have any of the conditions listed below?

	Yes	No	How old were you when you were first told you had this condition?
Cancer, of any type(s), *specify:*			
_____ *Type (First place where **1st** cancer started)*	____	____	_____ Years old
_____ *Type (First place where **2nd** cancer started)*	____	____	_____
Fibrocystic breasts, or other benign breast disease	____	____	_____
Colon polyps	____	____	_____
Ovarian cysts	____	____	_____
Hypertension or high blood pressure, *excluding during pregnancy*	____	____	_____
Diabetes	____	____	_____
Heart disease	____	____	_____
Hypothyroidism	____	____	_____
Hyperthyroidism	____	____	_____
Osteoporosis	____	____	_____
Fractures	____	____	_____
Depression	____	____	_____
Gallbladder disease	____	____	_____
Other condition(s), *specify:*			
_____	____	____	_____
_____	____	____	_____

19. Have you been treated with radiation therapy for any of the following reasons?

Reason for radiation therapy	**If yes:**		**At what sites have you had radiation therapy?**	**How old were you when you had radiation therapy?**
Acne	___ Yes	___ No		
Ringworm	___ Yes	___ No		
Enlarged gland	___ Yes	___ No		
Tonsils	___ Yes	___ No		
Other reason	___ Yes	___ No		
Specify other reason for radiation therapy, *other than for cancer:*				

20. If you have had cancer, which of the following treatments have you received?

If you have not had cancer, please check here _____ **and go to Question 21.**

Treatment for cancer			**If yes, how old were you when you had this treatment?**
Surgery	___ Yes	___ No	
Radiation therapy	___ Yes	___ No	
Chemotherapy	___ Yes	___ No	
Hormones *(for example Tamoxifen or Megace)*	___ Yes	___ No	
Other therapy	___ Yes	___ No	
Specify other therapy:			

21. Have you been exposed to the following dust, chemicals, or radiation?

Exposure				**If yes, how old were you when you were exposed?**
Silica	___ Yes	___ No	___ Unsure	
Asbestos	___ Yes	___ No	___ Unsure	
Vinyl choride	___ Yes	___ No	___ Unsure	
Aniline dyes	___ Yes	___ No	___ Unsure	
Radiation, other than for therapy *(for example, in work)*	___ Yes	___ No	___ Unsure	
Other exposure	___ Yes	___ No	___ Unsure	
Specify other exposure:				

22. Have you smoked at least 100 cigarettes in your life?

_____ Yes _____ No --- **Go to Question 28.**

23. How old were you when you FIRST STARTED smoking cigarettes regularly?

_____ Years old _____ Never smoked regularly --- **Go to Question 28.**

24. Do you smoke cigarettes now?

_____ Yes --- **Go to Question 26.** _____ No

25. How old were you when you LAST STOPPED smoking cigarettes? _____ Years old

26. On the average, how many cigarettes do/did you smoke per day?

_____ Cigarettes per day _____ Less than 1 cigarette per day

27. Considering how many times you may have stopped smoking and then restarted, how many TOTAL YEARS have you actually smoked cigarettes?

_____ Total years smoked cigarettes _____ Smoked less than 1 year

28. How many drinks of alcoholic beverages do you USUALLY have PER WEEK? *(Consider a drink to be a drink or shot of liquor, a 4 oz. serving of wine, or one 12 oz. can or bottle of beer, light beer, or a wine cooler).*

Check the usual number of drinks PER WEEK:

___ Never drink ___ Less than 1 ___ 1-3 ___ 4-6 ___ 7-14 ___ 15 or more

29. At what age did you have your first menstrual period? _____ Years old

30. What was the date of the beginning of your last menstrual period?

___ ___/___ ___/___ ___ ___ ___
Month Day Year

31. How many pregnancies have you had? _____

32. How many children have you given birth to? _____

33. How old were you when you had your first child? _____

34. Have you ever breast fed? _____ Yes _____ No --- **Go to Question 36.**

35. If yes, for how many total months have you breast fed all children? _____ Total months

36. Have you experienced menopause, either natural menopause or menopause caused by surgery or chemotherapy?

_____ Yes _____ No --- **Go to Question 40.**

37. If yes, how old were you when you experienced menopause? _____ Years old

38. Have you had a hysterectomy (has your uterus/womb been removed)?

_____ Yes _____ No --- **Go to Question 40.**

39. If yes, how old were you when you had a hysterectomy? _____ Years old

40. Has one or both of your ovaries been removed?

_____ Yes, **ONE** ovary removed; IF YES: How old were you? _____ Years old

_____ Yes, **BOTH** ovaries removed; IF YES: How old were you? _____ Years old

_____ No, ovaries were not removed

_____ Not sure if ovaries were removed

41. Have you ever used any of the following hormones?	**IF YES...**			
	Do you **CURRENTLY** use this hormone?	How old were you when you **FIRST** used this hormone?	In TOTAL, for how many **YEARS + MONTHS** have you used---or did you use---this hormone?	What are the **NAME(S)** of the hormone(s) you have used?
Birth control pills? ___ Yes ___ No	___ Yes ___ No	_____ Years old	_____ Years + _____ Months	
Fertility drugs? *(for example, Clomid or Pergonal/Metrodin)* ___ Yes ___ No	___ Yes ___ No	_____ Years old	_____ Years + _____ Months	
Estrogen, for symptoms of menopause? *(for example, Premarin)* ___ Yes ___ No	___ Yes ___ No	_____ Years old	_____ Years + _____ Months	NAMES: *Please CHECK all types of estrogen used:* Pills _____ Shots _____ Patch _____ Vaginal cream/gel or suppositories _____ Don't know _____ Other: _____
Progesterone or progestins, with estrogen for menopause? *(for example, Provera)* ___ Yes ___ No	___ Yes ___ No	_____ Years old	_____ Years + _____ Months	
Tamoxifen, to prevent breast cancer? ___ Yes ___ No	___ Yes ___ No	_____ Years old	_____ Years + _____ Months	**Tamoxifen**
Raloxifene, for osteoporosis, or for breast cancer prevention? ___ Yes ___ No	___ Yes ___ No	_____ Years old	_____ Years + _____ Months	**Raloxifene**
Other hormones? ___ Yes ___ No *Specify:* _____	___ Yes ___ No	_____ Years old	_____ Years + _____ Months	

42. Did your mother take diethylstilbestrol (DES), or estrogen, during any of her pregnancies?

_____ Yes _____ No

43. Have you ever had an ultrasound or sonogram of the ovaries?

_____ Yes, date of most recent: ___ ___/___ ___ or _____ No
Month *Year*

44. Have you ever had a blood test to measure CA125?

_____ Yes, date of most recent: ___ ___/___ ___ or _____ No
Month *Year*

45. Have you or any member of your family been diagnosed as having a condition called ataxia telangiectasia?

Yourself: ____ Yes ____ No

Your family members: ____ Yes ____ No

46. If yes, please list family members who have been diagnosed with ataxia telangiectasia, by their relation to you.

_____

47. Does any medical condition, other than cancer or ataxia telangiectasia, tend to run in your family?

_____ Yes _____ No --- **Go to Question 52.**

48. If yes, what medical condition(s) tend to run in your family? Please list conditions and family members who have or had the conditions, by their relation to you.

_____

_____

_____

_____

Questions 49-51 are for office use only --- Please go to Question 52.

52. How much did you weigh ten years ago? _____ Pounds

53. What is the most you ever weighed, when you were <u>not</u> pregnant? _____ Pounds

54. What occupation have you had for the longest period of time? _____

55. If you have had any of the x-rays or tests in the following table, please indicate the number of different times you had each x-ray or test during the specified age ranges. *If you are unsure when or how many times you had some x-rays or tests, please answer to the best of your memory.*

If you **NEVER HAD ANY** of the x-rays or tests listed, PLEASE CHECK HERE _____ **and go to Question 56.**

X-RAY or TEST	**Check if you NEVER HAD this x-ray or test**	**Number of times you had this x-ray or test in each age range** *(Please count the number of times only, not the number of individual films taken.)*			
		Up to Age 19	**Age 20-35**	**Age 36-49**	**Age 50 and older**
***For example,** if you had one chest x-ray at age 20, one at 40, and one at 42:*	____		***1***	***2***	
Chest x-ray	____				
Mammography	____				
X-ray of stomach	____				
Upper GI series	____				
Barium enema	____				
CAT or CT scan of head	____				
CAT or CT scan of chest or abdomen	____				
BONE X-RAYS *(Please specify:)* 1. _____					
2. _____					
3. _____					
4. _____	____				
Dental x-rays	____				
Bone scan	____				
Thyroid scan	____				
Angiogram	____				
Magnetic resonance imaging (MRI)	____				

56 Have you had other kinds of x-rays or similar tests that were not listed? _____ Yes _____ No ---- **Go to Question 58**

57. If yes, please indicate other x-rays or tests you had, and the number of different times you had these x-rays or tests.

OTHER X-RAY or TEST *Please specify:*	**Number of times you had this x-ray or test in each age range** *(Please count the number of times only, not the number of individual films taken.)*			
	Up to Age 19	**Age 20-35**	**Age 36-49**	**Age 50 and older**

58. Please list all medications, hormones, and nutritional supplements that you are CURRENTLY taking.

Medication, hormone, or nutritional supplement	**Dose**	**Number of times dose is taken each day**

Questionnaire for *men* who participate in the Breast Cancer Risk Study, JH9243

Principal Investigator and Associates:
Kathy J. Helzlsouer, MD, MHS, Nancy Davidson, MD, Emily Harris, MPH, PhD

This questionnaire includes general medical questions, and questions concerning occupational exposures and tobacco and alcohol use. Answering each question is completely voluntary---you may skip questions that you do not want to answer. However, we hope that you will answer the questionnaire as completely as possible. If you need more space to answer a question, please use the back of the page.

Your questionnaire will be kept confidential and will not be given to anyone who is not helping with this study. Please call Helen Perry at 410-614-1112 if you have questions about the questionnaire or the study. Thank you for helping us learn more about the causes of breast cancer.

Your questionnaire is a very important part of the study. If you need a new envelope to return your questionnaire to us, please call Helen Perry at 410-614-1112. We will be glad to send you an envelope. If you wish to post your own envelope, please return the questionnaire to us at:

Johns Hopkins School of Public Health
615 North Wolfe Street
Baltimore, MD. 21205
Attn: Dr. Kathy Helzlsouer
Dept. of Epidemiology, Room 6132

Questionnaire for Breast Cancer Risk Study, JH9243

1. Today's date: ___ ___ /___ ___ /___ ___ ___ ___
   Month Day Year

2. Your name:

   _____
   First, Middle, Last

3. Address: _____
   Street

   _____
   City State Zip Code

4. Daytime phone: (___ ___ ___) ___ ___ ___ - ___ ___ ___ ___

5. Evening phone: (___ ___ ___) ___ ___ ___ - ___ ___ ___ ___

6. Date of birth: ___ ___ /___ ___ /___ ___ ___ ___
   Month Day Year

7. Marital Status *(Circle):* Single Married Widowed Divorced

8. Please circle the highest number of years of education you completed:

   1 2 3 4 5 6 7 8 — 9 10 11 12 *Highschool* — 13 14 15 16 *College* — 16+ *Post graduate*

9. What is your race/ethnic background?

   _____ White, non-Hispanic
   _____ Asian/Pacific Islander
   _____ African American
   _____ American Indian
   _____ Hispanic/Latino
   _____ Other, please specify: _____

10. Are you of Ashkenazi Jewish (Eastern European or Russian Jewish) descent?

    _____ Yes _____ No

11. What are the ethnic backgrounds of your parents?

    Mother: _____ Father: _____

12. What is your height and weight?

Height: _____ Feet _____ Inches Current weight: _____ Pounds

13. How much did you weigh ten years ago? _____ Pounds

14. What is the most you ever weighed? _____ Pounds

15. Have you ever been told by a doctor or other health professional that you have any of the conditions listed below?

	Yes	No	How old were you when you were first told you had this condition?
Cancer, of any type(s), *specify:*			
_____ *Type (First place where **1st** cancer started)*	____	____	_____ Years old
_____ *Type (First place where **2nd** cancer started)*	____	____	_____
Colon polyps	____	____	_____
Hypertension or high blood pressure	____	____	_____
Diabetes	____	____	_____
Heart disease	____	____	_____
Hypothyroidism	____	____	_____
Hyperthyroidism	____	____	_____
Osteoporosis	____	____	_____
Fractures	____	____	_____
Depression	____	____	_____
Gallbladder disease	____	____	_____
Any problems with your breasts, *specify:*			
_____	____	____	_____
Any other condition(s), *specify:*			
_____	____	____	_____
_____	____	____	_____

16. Have you been treated with radiation therapy for any of the following reasons?

Reason for radiation therapy	If yes:		At what site(s) have you had radiation therapy?	How old were you when you had radiation therapy?
Acne	___ Yes	___ No		
Ringworm	___ Yes	___ No		
Enlarged gland	___ Yes	___ No		
Tonsils	___ Yes	___ No		
Other reason	___ Yes	___ No		
Specify other reason for radiation therapy, *other than for cancer:*				

17. If you have had cancer, which of the following treatments have you received?

If you have not had cancer, please check here _____ **and go to Question 18.**

Treatment for cancer			If yes, how old were you when you had this treatment?
Surgery	___ Yes	___ No	
Radiation therapy	___ Yes	___ No	
Chemotherapy	___ Yes	___ No	
Hormones *(for example Tamoxifen or Megace)*	___ Yes	___ No	
Other therapy	___ Yes	___ No	
Specify other therapy:			

18. Have you been exposed to the following dust, chemicals, or radiation?

Exposure				If yes, how old were you when you were exposed?
Silica	___ Yes	___ No	___ Unsure	
Asbestos	___ Yes	___ No	___ Unsure	
Vinyl choride	___ Yes	___ No	___ Unsure	
Aniline dyes	___ Yes	___ No	___ Unsure	
Radiation, other than for therapy *(for example, in work)*	___ Yes	___ No	___ Unsure	
Other exposure	___ Yes	___ No	___ Unsure	
Specify other exposure:				

19. Have you smoked at least 100 cigarettes in your life?

_____ Yes _____ No --- **Go to Question 25.**

20. If yes, how old were you when you FIRST STARTED smoking cigarettes regularly?

_____ Years old _____ Never smoked regularly --- **Go to Question 25.**

21. Do you smoke cigarettes now?

_____ Yes --- **Go to Question 23.** _____ No

22. How old were you when you LAST STOPPED smoking cigarettes? _____ Years old

23. On the average, how many cigarettes do/did you smoke per day?

_____ Cigarettes per day _____ Less than 1 cigarette per day

24. Considering how many times you may have stopped smoking and then restarted, how many TOTAL YEARS have you actually smoked cigarettes?

_____ Total years smoked cigarettes _____ Smoked less than 1 year

25. How many drinks of alcoholic beverages do you USUALLY have PER WEEK? *(Consider a drink to be a drink or shot of liquor, a 4 oz. serving of wine, or one 12 oz. can or bottle of beer, light beer, or a wine cooler).*

Check the usual number of drinks PER WEEK:

___ Never drink ___ Less than 1 ___ 1-3 ___ 4-6 ___ 7-14 ___ 15 or more

26. Have you had a vasectomy (male sterilization)?

_____ Yes _____ No --- **Go to Question 28.**

27. If yes, how old were you when you had a vasectomy? _____ Years old

28. A digital rectal exam is when a doctor inserts his finger in the rectum to check for problems such as an enlarged prostate gland or polyps. Have you ever had a digital rectal exam?

_____ Yes _____ No --- **Go to Question 30.**

29. If yes, how many years has it been since your last digital rectal exam?

_____ Less than one year _____ Two years

_____ One year _____ Three or more years

30. Have you ever had a PSA blood test to see if you had prostate cancer?

_____ Yes _____ No --- **Go to Question 33.**

31. Has your PSA blood test ever been abnormal?

_____ Yes _____ No

32. Has your PSA blood test been followed up by: *(Check all that apply.)*

_____ Not followed up _____ Surgical operation

_____ Ultrasound _____ Radiation treatment

_____ Biopsy _____ Hormone treatment

_____ Other follow-up test or treatment, *specify:* _____

33. Have you ever had a biopsy of the prostate?

_____ Yes _____ No --- **Go to Question 35.**

34. If yes, please complete the following table:

Year biopsy of prostate was done	**Result of biopsy**

35. Have you ever had prostate surgery, other than biopsies?

_____ Yes _____ No --- **Go to Question 37.**

36. If yes, please complete the following table:

Have you had the following prostate surgery?			**How old were you when you had this surgery?**
Transurethral Resection (TURP)	___ Yes	___ No	
Prostatectomy (removal of the prostate gland)	___ Yes	___ No	
Other prostate surgery	___ Yes	___ No	
Specify other surgery: _____			

37. Have you ever used any of the following hormones?	**IF YES...**			
	Do you **CURRENTLY** use this hormone?	How old were you when you **FIRST** used this hormone?	In TOTAL, for how many **YEARS + MONTHS** have you used---or did you use--- this hormone?	What are the **NAME(S)** of the hormone(s) you have used?
Testosterone? ___ Yes ___ No	___ Yes ___ No	_____ Years old	_____ Years + _____ Months	
Anabolic steroids? ___ Yes ___ No	___ Yes ___ No	_____ Years old	_____ Years + _____ Months	
Proscar (Finasteride)? ___ Yes ___ No	___ Yes ___ No	_____ Years old	_____ Years + _____ Months	**Proscar (Finasteride)**
Other hormones? ___ Yes ___ No				
Specify: _____	___ Yes ___ No	_____ Years old	_____ Years + _____ Months	Name: _____
Specify: _____	___ Yes ___ No	_____ Years old	_____ Years + _____ Months	Name: _____

38. Have you ever had any of the following tests to check for problems with your breasts? *(Check all that apply.)*

_____ Never had any tests to check breasts

_____ Physician checked for breast lumps

_____ Mammogram (x-ray of the breasts)

_____ Ultrasound or sonogram of the breasts

_____ Biopsy of the breasts

39. Have you or any member of your family been diagnosed as having a condition called ataxia telangiectasia?

Yourself:	____ Yes	____ No
Your family members:	____ Yes	____ No

40. If yes, please list family members who have been diagnosed with ataxia telangiectasia, by their relation to you.

_____

41. Does any medical condition, other than cancer or ataxia telangiectasia, tend to run in your family?

_____ Yes _____ No --- **Go to Question 43.**

42. If yes, what medical condition(s) tend to run in your family? Please list conditions and family members who have or had the conditions, by their relation to you.

_____

_____

_____

_____

43. What occupation have you had for the longest period of time? _____

44. If you have had any of the x-rays or tests in the following table, please indicate the number of different times you had each x-ray or test during the specified age ranges. *If you are unsure when or how many times you had some x-rays or tests, please answer to the best of your memory.*

If you **NEVER HAD ANY** of the x-rays or tests listed, PLEASE CHECK HERE _____ **and go to Question 45.**

X-RAY or TEST	Check if you NEVER HAD this x-ray or test	Number of times you had this x-ray or test in each age range *(Please count the number of times only, not the number of individual films taken.)*			
		Up to Age 19	Age 20-35	Age 36-49	Age 50 and older
For example, *if you had one chest x-ray at age 20, one at 40, and one at 42:*	____		*1*	*2*	
Chest x-ray	____				
Mammography	____				
X-ray of stomach	____				
Upper GI series	____				
Barium enema	____				
CAT or CT scan of head	____				
CAT or CT scan of chest or abdomen	____				
BONE X-RAYS *(Please specify:)* 1. _____					
2. _____					
3. _____					
4. _____	____				
Dental x-rays	____				
Bone scan	____				
Thyroid scan	____				
Angiogram	____				
Magnetic resonance imaging (MRI)	____				

45. Have you had other kinds of x-rays or similar tests that were not listed? _____ Yes _____ No ---- **Go to Question 47.**

46. If yes, please indicate other x-rays or tests you had, and the number of different times you had these x-rays or tests.

OTHER X-RAY or TEST	**Number of times you had this x-ray or test in each age range** *(Please count the number of times only, not the number of individual films taken.)*			
Please specify:	**Up to Age 19**	**Age 20-35**	**Age 36-49**	**Age 50 and older**

47. Please list all medications, hormones, and nutritional supplements that you are CURRENTLY taking.

Medication, hormone, or nutritional supplement	**Dose**	**Number of times dose is taken each day**

Family History Form for Breast Cancer Risk Study, JH9243

Principal Investigator and Associates:
Kathy J. Helzlsouer, MD, MHS, Nancy Davidson, MD, Emily Harris, MPH, PhD

Please record information about your relatives on the attached form, whether or not they have had cancer. **If you don't know all of the information requested, please include as much information as you know or can obtain.** For example, if you know only that your Grandfather was born between 1890 and 1900 and that he died in his late 70' s, **write "1890-1900" in the "DATE OF BIRTH" column, and "late 70's" in the "CURRENT AGE or AGE AT DEATH" column.**

By **"TYPE(S) OF CANCER"**, we mean the first place where a relative's cancer started, not where a cancer may have spread to at a later time. So if your Grandfather had colon cancer which spread to his liver, the type of cancer he had would be colon cancer, not liver cancer.

If you don't know and cannot obtain any information at all about when a relative was born, whether he or she had cancer, or any other information requested, **please put UNK, for unknown, or a question mark, in that column. Include first and last names of all relatives, and maiden names of female relatives who married.** If more space is needed, please use the back of the page.
Please call Helen Perry at 410-614-1112 if you have questions about the questionnaire or study. Thank you.

FAMILY HISTORY FORM FOR BREAST CANCER RISK STUDY, JH9243

YOUR NAME _____ Address _____

Date completed _____/_____/_____ JHH History # _____

FULL NAME OF RELATIVE Include Maiden Name	DATE OF BIRTH MO/DAY/YEAR	ANY CANCER FOUND? *YES /NO*	If YES, **AGE** CANCER WAS FOUND	TYPE(S) of CANCER FOUND *If breast cancer, one breast or both?*	OTHER ILLNESSES or MEDICAL CONDITIONS *that you know this relative has or had*	CURRENT AGE or AGE AT DEATH	IF DECEASED, CAUSE OF DEATH
YOUR SPOUSE	__/__/____						
YOUR MOTHER (Biological)	__/__/____						
YOUR FATHER (Biological)	__/__/____						
YOUR SISTERS Please mark with a * if not your full blood sister.							
1.	__/__/____						
2.	__/__/____						
3	__/__/____						
4.	__/__/____						
5.	__/__/____						
6.	__/__/____						

YOUR NAME _____

FULL NAME OF RELATIVE Include Maiden Name	DATE OF BIRTH MO/DAY/YEAR	ANY CANCER FOUND? *YES/ NO*	If YES, **AGE** CANCER WAS FOUND	TYPE(S) of CANCER FOUND *If breast cancer, one breast or both?*	OTHER ILLNESSES or MEDICAL CONDITIONS *that you know this relative has or had*	CURRENT AGE or AGE AT DEATH	IF DECEASED, CAUSE OF DEATH
YOUR BROTHERS	Please mark with a * if not your full blood brother.						
1.	__/__/____						
2.	__/__/____						
3.	__/__/____						
4.	__/__/____						
5.	__/__/____						
6.	__/__/____						
YOUR DAUGHTERS	Mark with a * if not your biological daughter.						
1.	__/__/____						
2.	__/__/____						
3.	__/__/____						
YOUR SONS	Mark with a * if not your biological son.						
1.	__/__/____						
2.	__/__/____						
3.	__/__/____						
Father of your biological children, if not your spouse	__/__/____						

YOUR NAME _____

FULL NAME OF RELATIVE Include Maiden Name	DATE OF BIRTH MO/DAY/YEAR	ANY CANCER FOUND? *YES/ NO*	If YES, **AGE** CANCER WAS FOUND	TYPE(S) of CANCER FOUND *If breast cancer, one breast or both?*	OTHER ILLNESSES or MEDICAL CONDITIONS *that you know this relative has or had*	CURRENT AGE or AGE AT DEATH	IF DECEASED, CAUSE OF DEATH
YOUR MOTHER'S SISTERS (Your Maternal Aunts) Mark with a * if not a full blood sister of your mother.							
1.	__/__/____						
2.	__/__/____						
3.	__/__/____						
4.	__/__/____						
5.	__/__/____						
6.	__/__/____						
YOUR MOTHER'S BROTHERS (Your Maternal Uncles) Mark with a * if not a full blood brother of your mother.							
1.	__/__/____						
2.	__/__/____						
3.	__/__/____						
4.	__/__/____						
5.	__/__/____						
6.	__/__/____						

YOUR NAME _____

FULL NAME OF RELATIVE Include Maiden Name	DATE OF BIRTH MO/DAY/YEAR	ANY CANCER FOUND? *YES / NO*	If YES, **AGE** CANCER WAS FOUND	TYPE(S) of CANCER FOUND *If breast cancer, one breast or both?*	OTHER ILLNESSES or MEDICAL CONDITIONS *that you know this relative has or had*	CURRENT AGE or AGE AT DEATH	IF DECEASED, CAUSE OF DEATH
YOUR FATHER'S SISTERS (Your Paternal Aunts) Mark with a * if not a full blood sister of your father.							
1.	__/__/____						
2.	__/__/____						
3.	__/__/____						
4.	__/__/____						
5.	__/__/____						
6.	__/__/____						
YOUR FATHER'S BROTHERS (Your Paternal Uncles) Mark with a * if not a full blood brother of your father.							
1.	__/__/____						
2.	__/__/____						
3.	__/__/____						
4.	__/__/____						
5.	__/__/____						
6.	__/__/____						

YOUR NAME _____

FULL NAME OF RELATIVE Include Maiden Name	YEAR OF BIRTH	ANY CANCER FOUND? *YES/NO*	If YES, **AGE** CANCER WAS FOUND	TYPE(S) of CANCER FOUND *If breast cancer, one breast or both?*	OTHER ILLNESSES or MEDICAL CONDITIONS *that you know this relative has or had*	CURRENT AGE or AGE AT DEATH	IF DECEASED, CAUSE OF DEATH
YOUR MOTHER'S PARENTS (Your Maternal Grandparents)							
Your Mother's Mother (Biological)							
Your Mother's Father (Biological)							
YOUR FATHER'S PARENTS (Your Paternal Grandparents)							
Your Father's Mother (Biological)							
Your Father's Father (Biological)							

Do you have other blood relatives who have had cancer? _____ Yes _____ No _____ Unsure

If yes, please provide information about your other relatives on the next page.

YOUR NAME _____

Your other blood relatives who have had cancer

On your **Mother's** side of the family

Name	Relation to you	DATE OF BIRTH MO/DAY/YEAR	AGE CANCER WAS FOUND	TYPE(S) of CANCER FOUND *If breast cancer, one breast or both?*	CURRENT AGE or AGE AT DEATH	IF DECEASED, CAUSE OF DEATH
		__/__/____				
		__/__/____				
		__/__/____				
		__/__/____				

On your **Father's** side of the family

		__/__/____				
		__/__/____				
		__/__/____				
		__/__/____				
		__/__/____				

Screening Form for Breast Cancer Risk Study, JH9243, Kathy J. Helzlsouer, PI *(Lavendar frm)*

Name: _____ DOB: _____ HX #: _____

Phone: _____ Physician/Clinic: _____ Date of Draw: _____

IF NOT DRAWN: *Date of visit:* _____ *Was this person: 1. Screened?* ____ *Yes* ____ *No*

2. Eligible? ____ *Yes* ____ *No* *3. Willing to participate today?* ____ *Yes* ____ *No*

If screened, eligible, and willing to participate today, why wasn't blood drawn? _____

Does this person want to participate at a later visit? ____ *Yes* ____ *No* ____ *Maybe*

All participants (1-2 must be Yes.) ***If participant is pregnant, father of child must sign consent.***	
1. Is this person at least 20 years old?	_____ Yes
2. Does this person have no hx of cancer, other than breast cancer or nonmelanoma skin cancer?	_____ Yes
Women dx with breast cancer (1-2 must be Yes.)	
1. Has this woman been diagnosed with invasive or in situ nonmetastatic breast cancer, in the last 6 months?	_____ Yes
2. Has she not yet started chemo or radiation? *(Tamoxifen/Megace/Other hormonal therapy are OK.)*	_____ Yes
Women with a family history of breast cancer, or with a biopsy (1 OR 2 must be Yes.)	
1. Does this woman have at least one first or two second degree relatives, on the same side of the family diagnosed with breast cancer?	_____ Yes
2. OR has she had a breast bx which showed proliferative disease, hyperplasia, atypia, or fibroadenoma?	_____ Yes
Relatives dx with brca: _____ First degree are parents, brothers, sisters, children. Second degree are grandparents, aunts, uncles, nieces, nephews. Questionnaires given to BOSS patients: Questionnaire _____ Addendum _____ Family Hx _____	
Control women (1-3 must be No.)	
1. Have any of this woman's first degree relatives been diagnosed with any cancer, other than nonmelanoma skin cancer, or prostate cancer diagnosed after age 80?	_____ No
2. Does she have more than one second degree relative on each side of the family dx'd with breast cancer?	_____ No
3. Has she ever had a breast biopsy, other than aspiration of a fluid-filled cyst only?	_____ No
Mother or father of a child diagnosed with AT, or employee who participated in 1993-5 (1 OR 2 must be Yes.)	
1. Is this person a mother or a father of a child who has been diagnosed with ataxia telangiectasia?	_____ Yes
2. Is this person an employee whose blood was assayed at NIH between 1993 and 1995?	_____ Yes

If blood is drawn, attach random number ID label here and on vacutainers.

Has this person previously given blood to the study, in 1997 or later?

_____ Yes _____ No

NAMID from Paradox: N _____

DATE

FIELD(INADD)

Dear FIELD(SALUT),

We are contacting you to ask for your help with our study of DNA Repair and Breast Cancer. We are interested in learning more about the causes of breast cancer. In particular, we are studying the relationship between possible susceptibility factors and environmental exposures and their link to breast cancer. You and your family members are being contacted because of the history of breast cancer in your family. Your name was given to us by your FIELD(familymem), FIELD(NAME).

The study involves completing a questionnaire and providing a blood sample. We will contact you by phone in about 3 weeks to discuss this study with you and to ask about your willingness to participate in the study. We have enclosed a return postcard that you may return to us if you do not wish to be called about participation in the study. Please feel free to contact me or Ms. Helen Perry at (410) 614-1112 if you have questions.

Sincerely,

Kathy J. Helzlsouer, M.D., M.H.S.
Associate Professor
Epidemiology and Oncology